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Brief Communications

Exclusion of Men from Randomized Phase III Breast Cancer Clinical Trials

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Male breast cancer treatment regimens are often extrapolated from female-based studies because of a paucity of literature analyzing male breast cancer. Using ClinicalTrials.gov, we analyzed breast cancer randomized clinical trials (RCTs) to determine which factors were associated with male-gender inclusion. Of 131 breast cancer RCTs identified, male patients represented 0.087% of the total study population, which is significantly less than the proportion of male patients with breast cancer in the U.S. (0.95%; $p < .001$). Twenty-seven trials included male patients (20.6%). Lower rates of male inclusion were seen in trials that randomized or mandated hormone therapy as part of the trial protocol compared with trials that did not randomize or mandate endocrine therapy (2.5% vs. 28.6% male inclusion; $p < .001$). It is imperative for breast cancer clinical trials to include men when allowable in order to improve generalizability and treatment decisions in male patients with breast cancer. ***The Oncologist*** 2020;25:e990–e992

Introduction

Breast cancer (BC) in men (any individual with primary male sex characteristics) accounts for 0.95% of all breast cancer cases diagnosed in the U.S. [1]. Men with BC receive similar treatments as women, with 96% undergoing mastectomy, 49% receiving radiotherapy, and 77% receiving adjuvant endocrine therapy [2]. BC in men is more likely to be estrogen/progesterone receptor positive as well as lower grade histologically [3]. However, male patients with BC tend to present with more advanced disease and have worse cancer-specific survival compared with female patients with BC [4, 5].

Male BC treatment regimens are often extrapolated from female-based studies because of limited literature about male BC, with most data arising from retrospective studies [6]. Subsequently, the Food and Drug Administration (FDA) recently published a draft guidance calling for BC trials to include men because of the lack of prospective data available to drive treatment recommendations [7]. To characterize the current sex profile of BC trials, we investigated the factors associated with male participation in BC studies by analyzing BC phase III randomized clinical trials (RCTs) and their eligibility criteria.

Materials and Methods

Breast cancer RCTs were identified through a search of ClinicalTrials.gov using the following parameters: terms, "cancer;" status, excluded "not yet recruiting;" phase, phase III; and study results, "with results." This search yielded 1,239 trials, which were screened for breast cancer–specific RCTs that addressed a therapeutic intervention (Fig. 1). Information regarding enrollment criteria was collected from ClinicalTrials.gov, the study protocol, and the primary publication of endpoint results (as available) for included trials. Two individuals independently performed trial screening and data collection. The total number and proportion of included male participants were reported for each trial and compared with the proportion of male patients with BC in the U.S. based on the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database [1]. Pearson's chi-square tests were used to assess factors that were associated with male inclusion in BC trials, and Wilcoxon signed rank tests were used to compare population and trial proportions of male patients with BC (SPSS, version 22.0).

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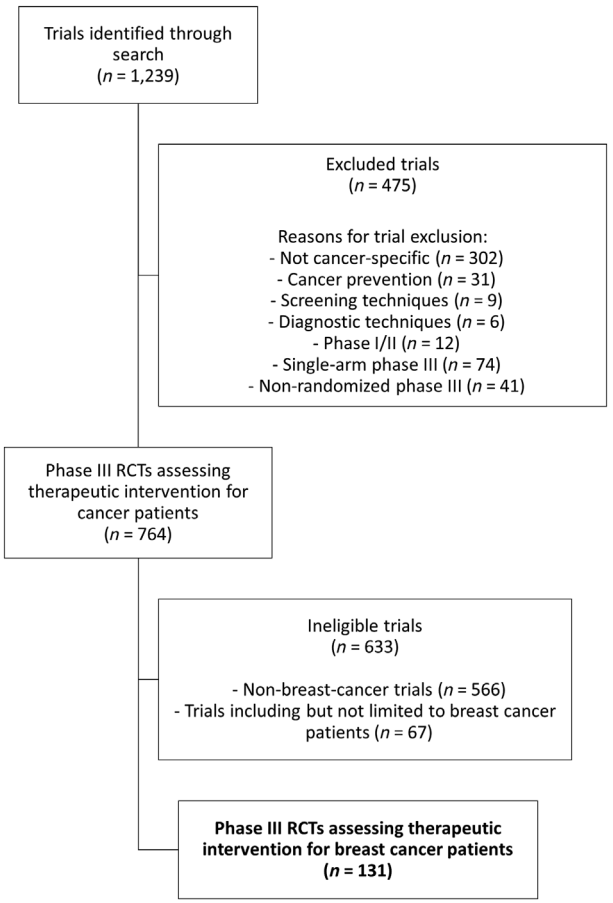

Figure 1. Flowchart of trial screening and eligibility.
Abbreviation: RCT, randomized clinical trial.

Results

One hundred thirty-one BC-specific RCTs were identified (Fig. 1). The total enrollment for these trials was 134,551 patients, of which 134,434 were female (99.913%) and 117 were male (0.087%). For 2018, SEER reported that the total proportion of male patients with breast cancer was 0.95% (2,550 male BC cases of 268,670 total BC cases) in the U.S. population [1]. Comparing the representation of male participants in BC clinical trials with the proportion of male patients with breast cancer in the U.S., men are significantly underrepresented in BC trials ($p < .001$).

Twenty-seven BC-specific RCTs (20.6%) allowed enrollment of men; of these 27 trials, the median proportion of patients enrolled who were men was 0.40% (interquartile range, 0.00%–0.74%). This median proportion of male enrollment was significantly lower than the population proportion of male patients with breast cancer (0.95%; $p = .001$). Higher rates of male inclusion in BC trials were noted among those that studied metastatic BC compared with nonmetastatic BC (29.7% vs. 11.1%; $p = .02$; Table 1). Higher rates of inclusion of men in BC trials were also seen in trials that investigated a targeted therapy (such as a small molecule inhibitor or monoclonal antibody) rather than cytotoxic chemotherapy (32.7% vs. 11.1%; $p = .02$; Table 1).

Trials that randomized hormone therapy or mandated hormone therapy as part of the study protocol were associated with excluding men compared with trials that did not randomize or mandate hormone therapy (2.5% vs. 28.6% male inclusion; $p < .001$; Table 1). Among the 91 trials that did not mandate hormone therapy or involve hormone therapy–related randomization, 65 (71.4%) excluded men in their study enrollment. Of these non–endocrine therapy trials that excluded men, none provided a rationale for the exclusion.

Several factors were not associated with allowing male enrollment in BC trials, including trials with industry sponsorship ($p = .87$) or cooperative group sponsorship ($p = .34$) and trials that met their primary endpoint ($p = .42$; Table 1).

Table 1. Factors associated with male inclusion in randomized controlled breast cancer trials

Factor	n/n_{total} (%)	Male inclusion, n/n_{total} (%)	p value[a]
Sex			
Female-only inclusion	104/131 (79.4)	—	—
All sex inclusion	27/131 (20.6)	—	—
Cancer stage			
Stages 0–III	45/131 (34.4)	5/45 (11.1)	Ref
Stage IV	64/131 (48.9)	19/64 (29.7)	.02
Not applicable or not listed	22/131 (16.8)	—	—
Systemic therapy[b]			
Cytotoxic chemotherapy	36/131 (27.5)	4/36 (11.1)	Ref
Targeted therapy	55/131 (42.0)	18/55 (32.7)	.02
Endocrine therapy			
No hormone therapy	91/131 (69.5)	26/91 (28.6)	Ref
Randomized or mandated hormone therapy	40/131 (30.5)	1/40 (2.5)	<.001
Industry sponsorship			
No	34/131 (26.0)	7/34 (20.6)	Ref
Yes	95/131 (72.5)	20/95 (21.0)	.87
Unknown	2/131 (1.5)	—	—
Cooperative group sponsorship			
No	45/131 (34.4)	12/45 (26.7)	Ref
Yes	86/131 (65.6)	15/86 (17.4)	.34
Trials that met their PEP			
No	50/131 (38.2)	11/50 (22.0)	Ref
Yes	54/131 (41.2)	9/54 (16.7)	.42
PEP pending	27/131 (20.6)	—	—

[a]For all included trials, the p value represents the results of a Pearson's chi-square test.
[b]Refers to randomized controlled trials with systemic therapy that studied as systemic therapy as the primary intervention.
Abbreviation: PEP, primary endpoint.

Discussion

This study provides an overview of male participation in BC phase III RCTs. Although male BC accounts for a minority of the total BC cases in the U.S., we found that men are greatly underrepresented in breast cancer RCTs. Trials studying metastatic BC and targeted therapy in BC were associated with inclusion of men. Other factors were associated with exclusion of men in breast cancer RCTs, including trials that randomized hormone therapy or mandated hormone therapy in their eligibility criteria.

Male BC is estrogen receptor positive in 92% of cases [2]. Men with hormone receptor–positive BC who receive adjuvant hormone therapy have the greatest overall survival [8]. However, only 77% of male patients with BC receive endocrine therapy [2]. This could be due to a variety of reasons, including insufficient guidelines and undesirable side effects [9]. One retrospective study showed that 50% of male patients with BC who received adjuvant hormone therapy experienced substantial side effects, most commonly hot flashes, decreased libido, and weight gain, causing nonadherence in approximately one quarter of patients [10]. The discrepancy between the proportion of men who need endocrine therapy and the proportion who receive it could also be due to the paucity of evidence regarding the efficacy of endocrine therapy in men. To determine optimal hormone therapy regimens, encourage adjuvant hormone therapy in male patients with BC, and provide guidance for providers, appropriate endocrine therapy trials should broaden their eligibility criteria and give men the opportunity to participate.

This study found not only that BC clinical trials exclude men at high rates but also that the nonendocrine trials do not provide a rationale for the exclusion. This is concerning given the increasing incidence [5, 11] of men with BC compared with women and the unchanging sex profile of BC trials. Along with the FDA's recent call for greater male inclusion in BC trials, these findings corroborate the importance of either including men in prospective BC trials or providing a rationale for male exclusion.

Our analysis has some limitations. First, we analyzed RCTs from a single registry, potentially missing RCTs from other trial registries. Additionally, no effort was made to contact trial investigators to discuss male exclusion, which may have clarified the rationale for sex-specific eligibility criteria.

Men are underrepresented in BC phase III clinical trials, especially trials studying endocrine therapy, leading to a paucity of existing data to support treatment decisions. As a result, men with BC are treated based on recommendations extrapolated from studies about female BC. Changing sex eligibility for BC trials is essential for improved treatment for men with BC.

Disclosures

C. David Fuller: Elekta AB (RF), Elekta, National Cancer Institute, American Association of Physicists in Medicine, European Society of Radiation Oncology, Tianjin Cancer Hospital, University Medical Center Groningen, Australia and New Zealand Head and Neck Cancer Society, International Association of Oral Oncology (H); **Benjamin D. Smith:** Varian Medical Systems (RF), Oncora Medical (IP). The other authors indicated no financial relationships.

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